

## REMARKS

Currently, claims 1, 3-6, 29-56 and 60-68 are pending in the present application. Claims 29-56 and 60-62 have been withdrawn. Claims 2, 7-28 and 57-59 have been canceled. Claims 1, 3, 63, 64 and 68 have been amended herein. The amendments to claims 1, 63 and 64 are supported by disclosure at page 3, paragraph 7 of the specification, which references U.S. Patent 5,385,929 (*see e.g.*, patent '929 at claims 5-11). The amendment to claim 3 is supported by the claim as originally filed. The amendment to claim 68 is supported by disclosure at page 10, lines 30-31 of the specification. No new matter has been added.

### **Claim Rejections**

#### **35 USC § 112, first paragraph**

Claims 1-6 and 63-68 remain rejected under 35 USC §112, first paragraph for lack of written description. The Examiner maintains that the specification does not provide adequate support for generic claims encompassing any atorvastatins hydroxylated in any positions in atorvastatin and any atorvastatin metabolites. The Examiner further asserts that the claims encompass more than the specific hydroxylated atorvastatin compounds disclosed in U.S. Patent 5,385,929 (the '929 patent). Applicant traverses.

As suggested by the Examiner, the claims have been amended according to 37 CFR 1.57(f) to recite the particular hydroxylated atorvastatin compounds disclosed in the '929 patent. Specifically, (2R-trans)-5-(4-fluorophenyl)-2-(1-methylethyl)-N-(4-hydroxyphenyl)-4-phenyl-1-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1H-pyrrole-3-carboxamide, (2R-trans)-5-(4-fluorophenyl)-2-(1-methylethyl)-N-(3-hydroxyphenyl)-4-phenyl-1-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1H-pyrrole-3-carboxamide, and (2R-trans)-5-(4-fluorophenyl)-2-(1-methylethyl)-N-(2-hydroxyphenyl)-4-phenyl-1-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1H-pyrrole-3-carboxamide. The material being inserted is the material previously incorporated by reference, and no new matter has been added.

In light of the amendments made herein, Applicant contends that the claims are adequately supported by the specification as filed, thereby satisfying the written

description requirement. Thus, Applicant respectfully requests reconsideration and withdrawal of this rejection.

**35 USC § 112, first paragraph**

Claim 68 remains rejected under 35 USC §112, first paragraph for scope of enablement. The Examiner maintains that while the specification enables the combination of amlodipine and atorvastatin metabolite further comprising the particular and specific antioxidants, it does not enable any substances or compounds represented by "an endogenous and/or exogenous antioxidant". Applicant traverses.

Claim 68 has been amended to recite that the antioxidants are lipophilic antioxidants. The term, lipophilic, provides chemical information that would allow one skilled in the art to elect suitable antioxidants to practice the instant invention. Therefore, the full scope of claim 68, as amended herein, is enabled, and Applicant requests reconsideration and withdrawal of this rejection.

**35 USC § 112, second paragraph**

Claims 2-3 remain rejected under 35 USC §112, second paragraph for indefiniteness. The Examiner states that "the recitation, 'derivative of amlodipine' renders claims 2-3 and 58-59 indefinite." Applicant disagrees.

Applicant reasserts the argument presented in the Response to Office Action filed September 6, 2005. However, solely in the interest of furthering prosecution, Applicant has canceled claim 2, and has amended claim 3 to delete the phrase "derivative of amlodipine". Claim 3 has also been amended to depend from claim 1, and continues to specify a particular derivative of amlodipine, namely amlodipine besylate. Therefore, Applicant contends that claim 3 is clear and definite, and this rejection should be withdrawn.

**35 USC § 103**

Claims 1-6 and 63-67 are rejected under 35 USC §103(a) as being unpatentable over WO95/05822 ('822) and US 5,383,929 [sic] ('929). According to the Examiner, '822 teaches amlodipine as effective in treating atherosclerosis, and '929 teaches hydroxylated-

atorvastatin compounds useful in inhibiting the biosynthesis of cholesterol. The '929 also teaches that inhibiting biosynthesis of cholesterol is useful in treating atherosclerosis and hypercholesterolemia. The Examiner concedes that the references do not expressly teach the hydroxylated-atorvastatin and amlodipine be incorporated together into a single composition. However, the Examiner argues that one of ordinary skill in the art would have been motivated to combine amlodipine and hydroxylated-atorvastatin together in a single composition because each is known to be useful in treating atherosclerosis. Applicant disagrees.

In order to establish a *prima facie* case of obviousness, "there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references) must teach or suggest all of the claim limitations." M.P.E.P. §2143, *see also, In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).

The compositions, as claimed herein, require that " . . . the effective amounts of amlodipine and hydroxylated atorvastatin metabolite synergistically inhibit lipid peroxidation in human low density lipoprotein or lipid membrane to achieve a therapeutic effect." (emphasis added) The combined disclosures of '822 and '929 do not teach or suggest a synergistic combination of amlodipine and metabolites of atorvastatin. Therefore, the references do not teach or suggest all of the claim limitations. Thus, the claimed compositions are nonobvious over '822 and '929.

Claim 68 is also rejected under 35 USC §103(a) as being unpatentable over '822 and '929, and further in view of Gilligan *et al.* (*J. Amer. College Card.*, 1994, 24(7):1611-17). According to the Examiner, the combination of '822 and '929 suggests the composition comprising amlodipine and hydroxylated atorvastatin, but does not expressly teach the further incorporation of antioxidant. Gilligan *et al.* teach that antioxidants such as Vitamin A, C, and E are known to be useful in the treatment of hypercholesterolemia in humans. Therefore, the Examiner concludes that it would have been obvious to one of ordinary skill in the art to incorporate vitamin A, C, and E into the composition of

amlodipine and hydroxylated-atorvastatin. "Combining two or more agents, which are known to be useful to treat atherosclerosis individually, into a single composition useful for the very same purpose is *prima facie* obvious, at least additive effect is expected." (OA at page 9). Applicants respectfully disagree.

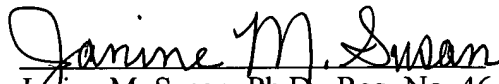
The instant specification teaches that the measured effect of the combination of drugs significantly exceeded any additive effects. (*See e.g.*, specification at page 4, paragraph 13.) The compositions of the claimed invention require synergistic inhibition of lipid peroxidation in human low density lipoprotein or lipid membrane to achieve a therapeutic effect." As argued above, the combination of '822 and '929 does not teach or suggest a synergistic combination of amlodipine and metabolites of atorvastatin. Adding the teachings of Gilligan *et al.* to those of '822 and '929 does not cure this defect. Therefore, the references do not teach or suggest all of the claim limitations. Thus, the claimed compositions are nonobvious over '822, '929 and Gilligan *et al.* Applicant requests reconsideration and withdrawal of the obviousness rejections.

In conclusion, in view of the above amendments and remarks, Applicant believes the pending claims are in condition for allowance and, therefore, requests that the Examiner issue a Notice of Allowance.

The Commissioner is authorized to charge any underpayment of fees to or credit any overpayment of fees to Deposit Account No. 03-2410.

The Examiner is invited to call the undersigned attorney at (617) 854-4069 should he determine that a telephonic interview would expedite prosecution of this case.

Respectfully submitted,

  
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